A Phase I, Open-Label Study To Assess The Safety, Feasibility and Engraftment of Zinc Finger Nucleases (ZFN) CCR5 Modified Autologous CD34+ Hematopoietic Stem/Progenitor Cells (SB-728MR-HSPC) with Escalating Doses of Busulfan In HIV-1 (R5) Infected Sub...

Grant Award Details

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Grant Type: Strategic Partnership III Track A

Grant Number: SP3A-07536

Project Objective: Stem cell gene therapy for HIV

Investigator:

Name:	John Zaia
Institution:	City of Hope, Beckman Research Institute
Type:	PI

Disease Focus: HIV/AIDS, Infectious Disease

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: $5,583,438

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: OM#1

View Report

Reporting Period: OM #2

View Report

Grant Application Details

Application Title: A Phase I, Open-Label Study to Assess the Safety, Feasibility and Engraftment of Zinc Finger Nucleases (ZFN) CCR5 Modified Autologous CD34+ Hematopoietic Stem/Progenitor Cells with Escalating Doses of Busulfan in HIV-1 (R5) Infected Subjects with Subop...

Public Abstract: The HIV-1 virus enters cells by binding to a protein called CCR5 on the cell surface. A naturally occurring mutation in CCR5, CCR5d32, has been shown to provide protection from HIV-1 infection and AIDS. All individuals carry two copies of the CCR5 gene, and those with both copies of CCR5 mutated are highly resistant to infection with HIV-1. Those carrying one mutated copy can get infected by HIV-1, but have a delayed progression to AIDS. Media and scientific magazines have discussed widely the case of the "Berlin patient," who was cured of his HIV-1 infection after receiving therapy for his leukemia with a blood stem cell transplant from a donor whose cells had both copies of CCR5 mutated. Other HIV-1 infected patients have not been treated in this way since donors must be a near-perfect tissue match with the patient and also have the double CCR5 mutation, two rare events which almost never happen together.

To mimic the effect of the CCR5 double mutation, we propose to create blood stem cells that have a double mutation in the CCR5 gene and then test this gene therapy method in patients. The patients' own blood stem cells will be treated in a process that can mutate the CCR5 gene, and then the stem cells will be transplanted back into the individual. These cells will carry the disrupted CCR5 gene and provide a renewable, long-lasting source of HIV-1 resistant immune cells. This novel strategy gets around the need to find a stem cell donor who carries the CCR5 double mutation and, since the stem cells come from the patient, there will be an ideal "perfect match" with no chance for rejection in the patient.

Results from mice transplanted with blood stem cells treated in this way have shown that the modified cells are functional and produce CCR5 mutant (HIV-1 resistant) progeny cells. When infected with HIV-1, these mice have reduced viral loads, and, importantly, the CCR5-disrupted CD4 cells have strong survival advantage. In the proposed clinical trial, HIV-1 infected patients with low levels of CD4 cells and no detectable HIV-1 while on antiviral medications will have their own blood stem cells modified at the CCR5 gene. Modified cells will then be re-infused into the patient after treatment with a chemotherapy agent, busulfan, which makes room for the stem cells to "take hold" in the marrow and generate an immune system with CCR5-mutant, HIV-1 resistant cells.

The applicant institution has worked with collaborating partners to develop this treatment method (a project funded by CIRM). They successfully developed this gene modification method up to the clinical testing phase. With combined expertise in stem cells, gene therapy, transplantation, treatment of HIV-related disease, this Strategic Partnership has the knowledge and skill to achieve all project goals.

Statement of Benefit to California:	California has the second highest number of persons living with HIV-1/AIDS in the United States. By the end of 2008, there were 100,366 adults and adolescents reported to be living with HIV-1 or AIDS in California (Cf. Scheer S et al, The Open AIDS Journal, 2012, 6(Suppl 1):188). This incidence translates into a medical and fiscal burden larger than any other state, except New York. A study from 2011 reported that public funding accounted for approximately $1.92 billion in HIV-1/AIDS services in California in the fiscal year 2008, of which the majority (90.4%) supported treatment (Cf. Leibowitz AA et al, J Acquir Immune Defic Syndr 2011;58:e11). In the fiscal year 2007-08, the California AIDS Drug Assistance Program (ADAP) served 32,842 clients and filled over 953,000 prescriptions for these clients. The Governor's current spending plan (2013-14 Budget Act) called for $448.4M to support this program, with sources coming from federal and California state funds. With these huge costs and HIV-1/AIDS being a life-long infection that requires compliant daily treatment medication for a lifetime, the need for a cure that has the potential to reduce the duration of antiviral therapy is substantial. Most importantly, such a therapy would significantly impact the quality of life of persons with HIV-1/AIDS. If successful, a stem cell-based therapy, though expensive as a single treatment, would significantly reduce the cost burden on the state and federal treatment programs and save money over the lifetime of a patient. The estimated cost of lifelong cART therapy is estimated to be $420,000 -$755,000 USD, with 73% of the cost going to cART drugs (Cf. Sloan CE et al. AIDS 2012, 26, 45). Conversion to generic first line combination cART drugs is estimated to only reduce costs by ~ $42,000/patient (Cf. Walensky R.P et al. Ann Intern Med 2013, 158, 84). Furthermore, not all patients with HIV-1 infection fully respond to the therapy; in fact, about one fifth of patients have an inadequate immune response despite keeping the virus at undetectable levels. These patients are at increased risk of infection and chronic diseases, which also impact the health spending of California. There is no treatment for such patients and, if successful, the cellular therapy derived from genetically modified blood stem cells proposed here would have a major impact on patient management and outcome. Success of this therapy would establish the safety of a possible future cure for HIV-1/AIDS. Added benefits are: 1) this stem cell-based gene therapy for HIV-1/AIDS will have a positive impact on the overall field of stem cell research with application to other diseases; 2) this demonstrates the progression of new technology supported by CIRM to the clinic, and 3) the technology was derived from California-based industry and success should have a positive economic impact in the state.